January 2021

An improved process for the preparation of Cysteamine Bitartrate

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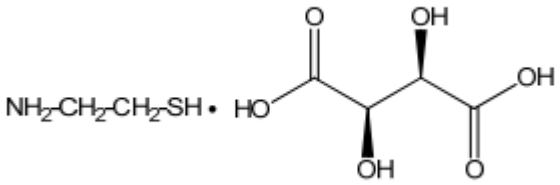
Field of the invention:

The present invention relates to an improved process for the preparation of 2-aminoethanethiol bitartrate which is represented by the following structural formula-1a.

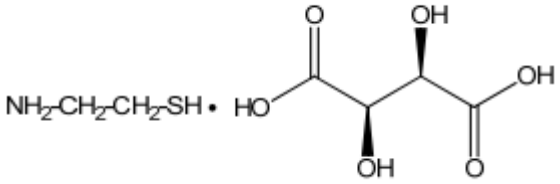


Formula-1a

The present invention also provides an improved process for the preparation of crystalline form of the compound of formula-1a herein after designated as crystalline form-M.

Background of the invention:

2-aminoethanethiol bitartrate is commonly known as Cysteamine bitartrate, which was approved in US & Europe under the brand names of Cystagon and Procysbi for the treatment of nephropathic cystinosis.



Formula-1a

The prior art processes for the preparation of Cysteamine bitartrate were broadly categorized into two methods.

In the first method, Cysteamine free base was directly converted to Cysteamine bitartrate.

In the second method, Cysteamine free base is first converted to its hydrochloride salt and then converted to its bitartrate salt.

The above said methods suffer with several disadvantages:

- Cysteamine free base is hygroscopic and thiol group present in Cysteamine is extremely susceptible to oxidation and forming the corresponding Cystamine impurity by auto oxidation when exposed to moisture, light or heat. The speed of oxidation of thiol group may increase through the effect of heat and light.
- Because of its high solubility in water it is very difficult to isolate Cysteamine in free base form the reaction mixture. This results in low yield.
- In above methods for the synthesis of Cysteamine bitartrate, there is chance of formation of Cystamine impurity when exposed to moisture, light or heat which results in lower yield and purity.
- To get pure Cysteamine, further purifications are required. This makes the process less attractive on commercial scale.

The present inventors have developed an improved process for the preparation of compound of formula-1a by overcoming the above said drawbacks to provide high yields and purity.

The present invention also provides an improved process for the preparation of crystalline form of the compound of formula-1a, herein after designated as crystalline form-M.

Brief description of the invention:

The first embodiment of the present invention provides an improved process for the preparation of Cysteamine bitartrate.

The second embodiment of the present invention provides a process for the preparation of crystalline form of Cysteamine bitartrate, herein after designated as crystalline form-M.

Advantages of the present invention:

- Provides the eco-friendly and cost-effective process.
- Provides high yields and purity.
- The present invention process is simple and avoids the isolation of Cysteamine free base.

- The present invention provides the formation of Cysteamine bitartrate directly from the compound of formula-2 with out the formation of Cysteamine free base. With this process Cystamine impurity formation is reduced to minimal level.
- The present invention process avoids the extra purifications steps.

Brief description of the drawings:

Figure-1: Illustrates the powder X-Ray diffraction pattern of crystalline form-M of Cysteamine bitartrate.

Figure-2: Illustrates the powder X-Ray diffraction pattern of Cysteamine bitartrate obtained according to Example-4.

Figure-3: Illustrates the powder X-Ray diffraction pattern of Cysteamine hydrochloride obtained according to Example-12.

Detailed description of the invention:

As used herein the term "suitable solvent" or solvent used in the present invention refers to "hydrocarbon solvents" such as n-hexane, n-heptane, cyclohexane, pet ether, benzene, toluene, pentane, cycloheptane, methyl cyclohexane, ethylbenzene, m-, o-, or p-xylene, or naphthalene and the like; "ether solvents" such as dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, t-butyl methyl ether, 1,2-dimethoxy ethane and the like; "ester solvents" such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; "polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutylketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; "alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1,2-propanediol (propylene glycol), 2-methoxyethanol, l, 2-

ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol and the like; "polar solvents" such as water or mixtures thereof.

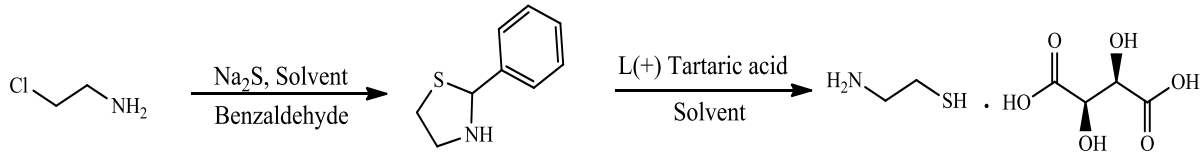
The first embodiment of the present invention provided an improved process for the preparation of Cysteamine bitartrate comprising:

a) reacting 2-chloroethanamine or its salt with benzaldehyde in presence of sodium sulfide in a solvent to provide 2-phenylthiazolidine of formula-2,
b) reacting 2-phenylthiazolidine of formula-2 with tartaric acid in a solvent to provide Cysteamine bitartrate of formula-1a,
c) optionally purifying Cysteamine bitartrate of formula-1a obtained in step-b).

Solvent in step-a) and step-b) selected form alcohol solvents, chloro solvents, ester solvents, ether solvents, ketone solvents, nitrile solvents, hydrocarbon solvents, polar aprotic solvents, polar solvents, water and mixtures thereof.

In the above process, step a) or step-b) optionally can be performed under an inert atmosphere of argon or nitrogen atmosphere or in presence of an antioxidant. Wherein, antioxidant is selected from butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), L-ascorbic acid and the like.

First embodiment of the present invention is schematically represented as follows:



2-chloroethanamine Formula-2 Cysteamine bitartrate

The second embodiment of the present invention provided a process for the preparation of crystalline form of Cysteamine bitartrate, herein after designated as crystalline form-M comprising:

a) providing a solution of Cysteamine bitartrate in a solvent,
b) isolating crystalline form-M of Cysteamine bitartrate.

A solution of Cysteamine bitartrate in step-a) can be obtained by dissolving at a temperature ranging from about 25°C to reflux temperature of the solvent used or can be obtained from the reaction mixture in the preparation of Cysteamine bitartrate. Solvent in step-a) is selected from methanol, isopropyl alcohol, sethanol, 2-butanol, water and mixtures thereof; isolating crystalline form-M in step-b) is by solvent removal by known techniques which are selected from cooling the mixture to lower temperatures to precipitate the solid followed by filtration of the mixture, crystallization; or by distillation of the solvent; or by combining with an anti-solvent.

In the above process, step a) or step-b) optionally involve seeding with crystalline form-M of Cysteamine bitartrate.

In the above process, step a) optionally can be performed under an inert atmosphere of argon or nitrogen atmosphere or in presence of an antioxidant. Wherein, antioxidant is selected from butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), L-ascorbic acid and the like.

An aspect of the second embodiment provides crystalline form-M of Cysteamine bitartrate characterized by its powder X-Ray difractogram substantially in accordance with figure-1.

The crystalline form-M of Cysteamine bitartrate of the present invention is prepared by the processes as illustrated in the present invention and they are useful for the preparation of various pharmaceutical compositions formulated in a manner suitable for the route of administration to be used where at least a portion of Cysteamine bitartrate is present in the composition in particular polymorphic form mentioned.

The third embodiment of the present invention provides the use of crystalline form-M of Cysteamine bitartrate for the preparation of pharmaceutical formulations.

The fourth embodiment of the present invention provides pharmaceutical composition comprising crystalline form-M of Cysteamine bitartrate and at least one pharmaceutically acceptable excipient. As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions,

emulsions, granules, capsules, suppositories, or injection preparations.

An aspect of fourth embodiment provides a pharmaceutical composition comprising crystalline form prepared according to the present invention and one or more pharmaceutically acceptable carriers for the treatment of nephropathic cystinosis.

The fifth embodiment of the present invention provided another improved process for the preparation of Cysteamine bitartrate comprising:

a) reacting ethanolamine with sulfuric acid in presence or absence of a phase transfer catalyst to provide compound of formula-3,
b) reacting compound of formula-3 with compound of formula-4 in presence of aqueous sodium hydrogensulfide, catalyst, base to provide compound of formula-5,
c) treating the compound of formula-5 with L(+)-tartaric acid in a solvent to provide Cysteamine bitartrate of formula-1a,
d) optionally purifying Cysteamine bitartrate of formula-1a.

Solvent in step-a) and step-c) are selected form alcohol solvents, chloro solvents, ester solvents, ether solvents, ketone solvents, nitrile solvents, hydrocarbon solvents, polar aprotic solvents, polar solvents, water and mixtures thereof. Base in step-b) is inorganic base.

The process of step-b) optionally carried out in a solvent selected from alcohol solvents, chloro solvents, ester solvents, ether solvents, ketone solvents, nitrile solvents, hydrocarbon solvents, polar aprotic solvents, polar solvents, water and mixtures thereof.

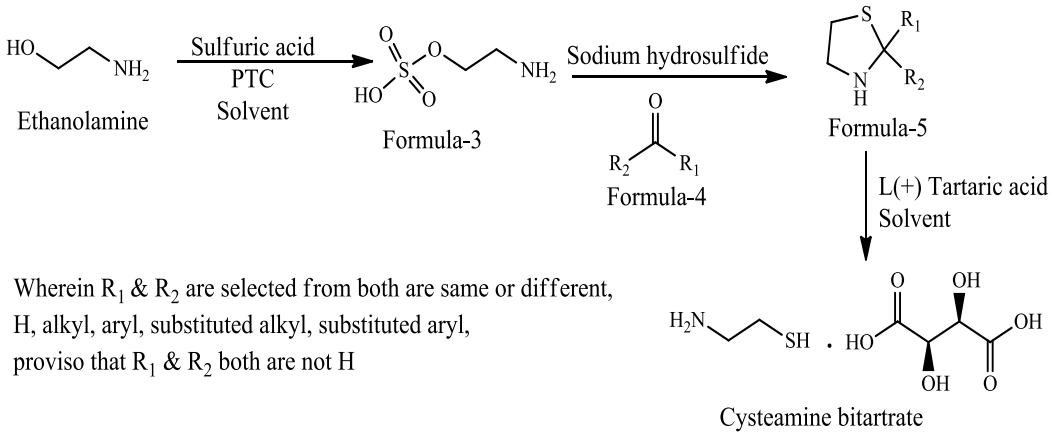
The phase transfer catalyst in step-a) selected from tetra-n-butyl ammonium bromide, triethyl benzyl ammonium chloride, tributyl benzyl ammonium chloride, trimethyl benzyl ammonium chloride, tetrabutylammonium bromide, tetrabutylammonium iodide, tetrabutylammonium hydrogen sulfate, tetrabutylammonium fluoride trihydrate, tetrabutylammonium fluoride, and tetrabutylammonium chloride

Catalyst in step-b) selected from para-toluene sulfonic acid.

In the above process, step a) or step-b) optionally can be performed under an inert atmosphere of argon or nitrogen atmosphere or in presence of an antioxidant. Wherein, antioxidant is selected from butylated hydroxytoluene (BHT), butylated hydroxyanisole

(BHA), L-ascorbic acid and the like.

Fifth embodiment of the present invention is schematically represented as follows:



Sixth embodiment of the present invention provided purification process for the Cysteamine bitartrate, comprising:

a) dissolving Cysteamine bitartrate in a solvent,

b) isolating pure of Cysteamine bitartrate.

Dissolution Cysteamine bitartrate in a solvent in step-a) at a temperature ranging from about 25°C to reflux temperature of the solvent used or can be obtained from the reaction mixture in the preparation of Cysteamine bitartrate. Solvent in step-a) is selected from methanol, ethanol, 2-butanol, water and mixtures thereof; isolating crystalline form-M in step-b) is by solvent removal by known techniques which are selected from cooling the mixture to lower temperatures to precipitate the solid followed by filtration of the mixture, crystallization; or by distillation of the solvent; or by combining with an anti-solvent wherein anti-solvent is isopropanol {isopropyl alcohol}.

In an aspect, in the above process optionally combining 0.1 to 0.3 moles equivalents of L-(+)-tartaric acid can be added to the solvent taken in step-a) before adding cysteamine bitartrate.

"Pure" or "substantially pure" means cysteamine bitartrate compound of formula-1a prepared by the process of the present invention is substantially free from the impurities. Cysteamine bitartrate obtained according to the present invention is having a purity of greater than about 98%, preferably greater than about 99%, more preferably greater than about 99.5% measured by HPLC [High Performance Liquid Chromatography].

The impurities, starting materials and by-products formed during the synthesis of Cysteamine bitartrate are well controlled as per ICH guide lines.

Crystalline form-M of Cysteamine bitartrate produced by the processes of the present invention can be further micronized or milled to get desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include but not limited to single or multi-stage micronization using cutting mills, pin/cage mills, hammer mills, jet mills, fluidized bed jet mills, ball mills and roller mills. Milling or micronization may be performed before drying or after drying of the product.

Cysteamine bitartrate obtained according to the present application is Crystalline form-M and is monohydrate.

Crystalline form-M of Cysteamine bitartrate obtained according to the present invention has particle size of less than about 250 µm or less than about 200 µm or less than about 150 µm or less than about 100 µm or less than about 50 µm or any other suitable particle sizes.

HPLC {High Pressure Liquid Chromatography} Method of Analysis:

Method-1:

Cysteamine bitartrate and its related substances were analyzed by HPLC with the following chromatographic conditions:

Apparatus: A liquid chromatograph is equipped with variable wavelength UV Detector and integrator. Column: X-Bridge C18 150 X 4.6mm, 3.5µm (Or) Equivalent; Wavelength: 205

nm; Column temperature: 25°C; Injection volume: 10 µL; Elution: Gradient; Diluent: Acetonitrile: Water.

Buffer Preparation:

i) Accurately transfer 1000 ml of milli-Q water into a suitable cleaned and dry beaker.
ii) Weigh 1.36 g of Potassium dihydrogen ortho phosphate and 2.0 g of 1-Octane sulfonic acid sodium salt anhydrous into 1000ml of milli-Q water and sonicate to dissolve, adjust its pH 2.6 with dilute ortho phosphoric acid
iii) Filter the obtained solution through 0.22 µm PVDF membrane filter paper and sonicate.

Mobile phase-A: Buffer 100%; Mobile phase-B: Acetonitrile: Water; Sample concentration: 20 mg/ml.

Method-2:

Cysteamine bitartrate and its related substances were analyzed by HPLC with the following chromatographic conditions:

Apparatus: A liquid chromatograph is equipped with variable wavelength UV Detector and integrator. Column: X-Bridge C18 150 X 4.6mm, 3.5µm (Or) Equivalent; Wavelength: 210 nm; Column temperature: 40°C; Injection volume: 15 µL; Elution: Gradient; Diluent: Water.

Buffer Preparation:

i) Accurately transfer 1000 ml of milli-Q water into a suitable cleaned and dry beaker.
ii) Weigh 5.0 g of 1-Octane sulfonic acid sodium salt anhydrous and 4.40g of Sodium dihydrogen phosphate monohydrate into 1000 milli-Q water and sonicate to dissolve, adjust its pH 2.6 with dilute ortho phosphoric acid
iii) Filter the obtained solution through 0.22 µm PVDF membrane filter paper and sonicate to degas it.

Mobile phase-A:- Buffer: Acetonitrile: Methanol;

Mobile phase-B:- Acetonitrile:Water:Methanol;

Sample concentration: 30 mg/ml.

PXRD (Powder X-Ray diffractogram) Method of Analysis:

The PXRD analysis of compounds of the present invention was carried out by using BRUKER-Axis/D8 ADVANCE (DAVINCI) X-Ray diffractometer using CuKα radiation of wavelength 1.5406A° and at a continuous scan speed of 0.03°/min.

The best mode of carrying out the present invention is illustrated by the below mentioned examples. These examples are provided as illustration only and hence should not be considered as limitation of the scope of the invention.

Examples:

Example-1: Preparation of 2-phenylthiazolidine compound of formula-2

Benzaldehyde (184.2 g) followed by sodium sulfide nonahydrate (248.5 g) were slowly added to the solution of 2-chloroethanamine hydrochloride (200 g) in water (280 ml) at 25-30°C and stirred the reaction mixture for 10 minutes at the same temperature. Heated the reaction mixture to 95-100°C and stirred the reaction mixture for 4 hours at the same temperature. Cooled the reaction mixture to 25-30°C and stirred the reaction mixture for 45 minutes at the same temperature. Filtered the solid and washed with water. Water and cyclohexane were added to the above obtained solid at 25-30°C and stirred the mixture for 10 minutes at the same temperature. Heated the mixture to 55-60°C and stirred the mixture for 45 minutes at the same temperature. Cooled the mixture to 25-30°C and stirred the mixture for 45 minutes at the same temperature. Filtered the solid, washed with cyclohexane and dried to get the title compound.

Yield: 140 g, Purity by HPLC: 99.0%.

Example-2: Preparation of Cysteamine bitartrate

2-phenylthiazolidine (20 g) was added to a solution of L(+) tartaric acid (20 g) in water (600 ml) at 25-30°C and stirred the reaction mixture for 10 minutes at the same temperature. Heated the reaction mixture to 95-100°C and stirred the reaction mixture in presence of nitrogen gas bubbling for 4 hours at the same temperature. Distilled off the solvent completely from the reaction mixture and co-distilled with cyclohexane and methanol. Dissolved the obtained compound in methanol at 70-75°C. Cooled the solution to 25-30°C and ethanol was added to the solution. Further cooled the mixture to -25 to -20°C and stirred

the mixture for 90 minutes at the same temperature. Filtered the precipitated solid, washed with ethanol and dried to get the title compound.

Yield: 22 g.

Example-3: Preparation of crystalline form-M of Cysteamine bitartrate

Dissolved the Cysteamine bitartrate (140 g) in methanol (1120 ml [degassed with nitrogen]) at 50-55°C and stirred for 15 minutes at the same temperature. Filtered the solution for particle free. Isopropanol (700 ml) was added to the filtrate at 25-30°C. Cooled the mixture to 5-10°C and stirred it for 3 hours at the same temperature. Filtered the precipitated solid, washed with the mixture of methanol and isopropanol and dried to get the title compound.

Yield: 107 g. PXRD of the obtained compound is as illustrated in figure-1.

M.R: 70-75°C.

Example-4: Purification of Cysteamine bitartrate

Dissolved the Cysteamine bitartrate (10 g) in methanol (50 ml) at 25-30°C and stirred for 25 minutes at the same temperature. Distilled off the solvent completely from the mixture and co-distilled with methanol dried to get the title compound.

Yield: 10 g. PXRD of the obtained compound is as illustrated in figure-2.

Example-5: Preparation of Cysteamine bitartrate

2-phenylthiazolidine (25 g) and butylated hydroxytoluene (1.6 g) were added to a solution of L(+) tartaric acid (25 g) in water (375 ml) at 25-30°C and stirred the reaction mixture for 10 minutes at the same temperature. Heated the reaction mixture to 95-100°C and stirred the reaction mixture for 2½ hours at the same temperature. Distilled off the solvent completely from the reaction mixture and co-distilled with isopropanol. Dissolved the obtained compound in water at 70-75°C. Cooled the solution to 25-30°C and isopropanol was added to the solution and stirred the mixture for 30 minutes at the same temperature. Filtered the precipitated solid, washed with isopropanol and dried to get the title compound.

Yield: 26.5 g.

Example-6: Preparation of Cysteamine bitartrate

2-phenylthiazolidine (50 g) was added to a solution of L(+) tartaric acid (49.9 g) in water (750 ml) at 25-30°C and stirred the reaction mixture for 10 minutes at the same temperature. Heated the reaction mixture to 95-100°C under distillation mode and stirred the reaction

mixture for 6 hours at the same temperature. Distilled off the solvent completely from the reaction mixture and co-distilled with isopropanol. Dissolved the obtained compound in water at 70-75°C. Cooled the solution to 25-30°C and isopropanol was added to the solution and stirred the mixture for 30 minutes at the same temperature. Filtered the precipitated solid, washed with isopropanol and dried to get the title compound.

Yield: 58 g.

Example-7: Preparation of 2-aminoethyl hydrogensulfate

Sulfuric acid (72.4 ml) was slowly added to the pre-cooled mixture of toluene (450 ml), ethanolamine (75 g), tetra-n-butylammonium bromide (75 g) at 10-15°C and stirred for 15 minutes at 25-30°C. Heated the reaction mixture to 105-110°C and stirred the reaction mixture under azeotropic conditions. Cooled the reaction mixture to 25-30°C and isopropyl alcohol was added at 25-30°C and stirred. Filtered the solid, washed with isopropyl alcohol. Slurried the compound in isopropyl alcohol and filtered to get the titled compound.

Example-8: Preparation of 2-methyl 2-ethylthiazolidine of formula-5 [R_1=Et, R_2=Me]

Sodium hydroxide (44.2 g) was added to the mixture of 2-aminoethyl hydrogensulfate obtained in Example-7, aqueous sodium hydrosulfide (619 ml), methyl ethyl ketone (396 ml) at 25-30°C. P-toluene sulfonic acid monohydrate was added to the above mixture at 25-30°C. Heated the reaction mixture to 80-85°C and stirred the reaction mixture at the same temperature. Cooled the mixture to 25-30°C and stirred. Filtered the mixture, washed with methyl ethyl ketone. Separated the organic layer from the obtained filtrate and the aqueous layer was extracted with methyl ethyl ketone. Combined the organic layers, washed with aqueous sodium hydroxide solution and organic layer was slurried with sodium chloride. Distilled off solvent completely from the organic layer to get the title compound.

Example-9: Preparation of Cysteamine bitartrate monohydrate.

2-methyl 2-ethylthiazolidine obtained in example-8 was slowly added to the mixture of L-(+)-tartaric acid (136 g), isopropyl alcohol (1080 ml) and water (216 ml) at 25-30°C under nitrogen atmosphere and stirred at the same temperature. Filtered the precipitated solid, washed with isopropyl alcohol and dried to get the title compound.

Yield: 150 g. PXRD of the obtained product is similar to the figure-1. Purity by HPLC: 99.85%, Dimer impurity {Cystamine impurity}:0.09%.

Example-10: Purification of Crystalline form-M of Cysteamine bitartrate hydrate

Nitrogen gas purged into water (250 ml) at 25-30°C. L(+)-Tartaric acid (7.6 g) was added to it and stirred under nitrogen atmosphere. Cysteamine bitartrate (125 g) was added to it and stirred. Filtered the solution and washed with the mixture of water and isopropyl alcohol. Isopropyl alcohol (1187.5 ml) was added to the obtained filtrate. Cooled the mixture to 7-10°C and stirred at the same temperature. Filtered the precipitated solid, washed with isopropyl alcohol and dried to get the title pure compound.

Yield: 109 g. PXRD of the obtained product is similar to the figure-1. Purity by HPLC: 99.85%, Dimer impurity {Cystamine impurity}:0.08%.

Example-11: Preparation of cysteamine hydrochloride

Step-a): Sulfuric acid (29 ml) was slowly added to the pre-cooled mixture of toluene (450 ml), ethanolamine (30 g), tetra-n-butylammonium bromide (30 g) at 10-15°C and stirred for 15 minutes at 25-30°C. Heated the reaction mixture to 105-110°C and stirred the reaction mixture under azeotropic conditions. Cooled the reaction mixture to 25-30°C and isopropyl alcohol was added at 25-30°C and stirred. Filtered the solid, washed with isopropyl alcohol. Slurried the compound in isopropyl alcohol and filtered to get 2-aminoethyl hydrogen sulfate.

Step-b): Sodium hydroxide (17.7 g), 30% aqueous sodium hydrosulfide (248 ml) and para-toluenesulfonic acid monohydrate (100 mg) were added to the mixture of 2-aminoethyl hydrogensulfate in methyl ethyl ketone (160 ml) at 25-30°C. Heated the reaction mixture to 80-85°C and stirred the reaction mixture at the same temperature. Cooled the mixture to 25-30°C and stirred. Filtered the mixture, washed with methyl ethyl ketone. Separated the organic layer from the obtained filtrate and the aqueous layer was extracted with methyl ethyl ketone. Combined the organic layers, washed with aqueous sodium hydroxide solution and organic layer was washed with aqueous sodium chloride solution. Distilled off solvent completely from the organic layer to get 2-methyl-2-ethylthiazolidine.

Step-c): Concentrated hydrochloric acid (43 ml) was slowly added to the mixture of 2-methyl 2-ethylthiazolidine and water at 25-30°C, heated the reaction mixture to 90-95°C and stirred. Distilled of the solvent and cooled to 75-80°C. Co-distilled with isopropanol and further cooled to 25-30°C. Isopropanol was added to obtained compound, cooled to the mixture to 0-

5°C and stirred. Filtered the precipitated solid, washed with isopropyl alcohol and dried to get the title compound.

Yield: 35 g

Example-12: Purification of cysteamine hydrochloride

Dissolved Cysteamine hydrochloride (40 g) in isopropanol (360 ml) at 45-50°C. Filtered the solution and washed with the isopropyl alcohol. Isopropyl alcohol (1187.5 ml) was added to the obtained filtrate. Cooled the filtrate to 5-10°C and stirred at the same temperature. Filtered the precipitated solid, washed with isopropyl alcohol and dried to get the title pure compound.

Yield: 30 g; PXRD of the obtained product is similar to the figure-3.

Drawings

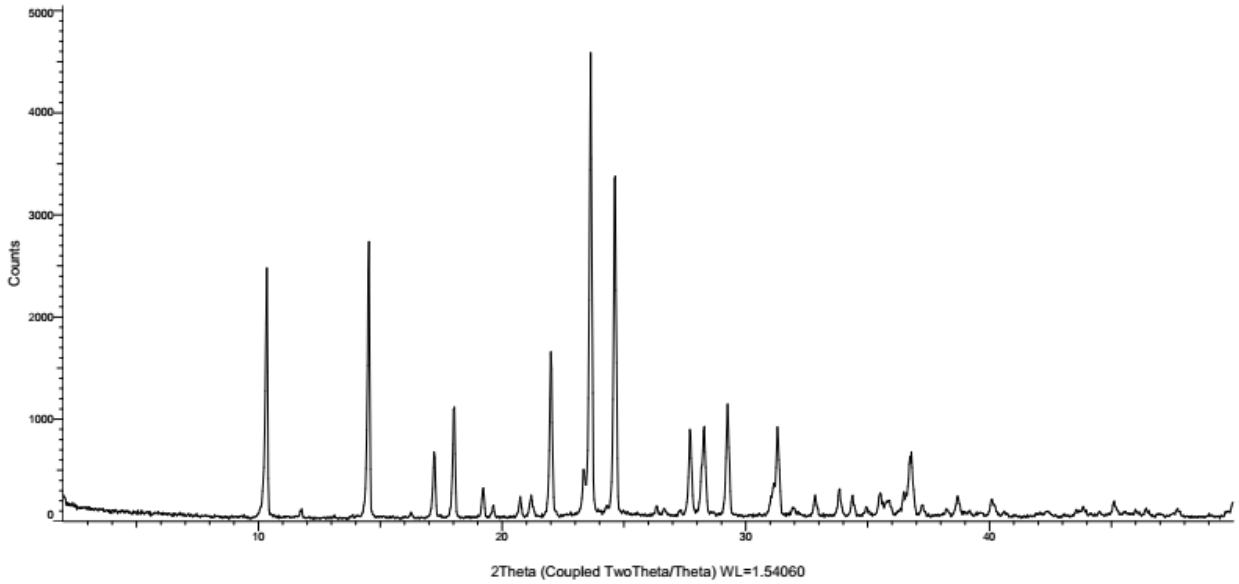


Figure-1

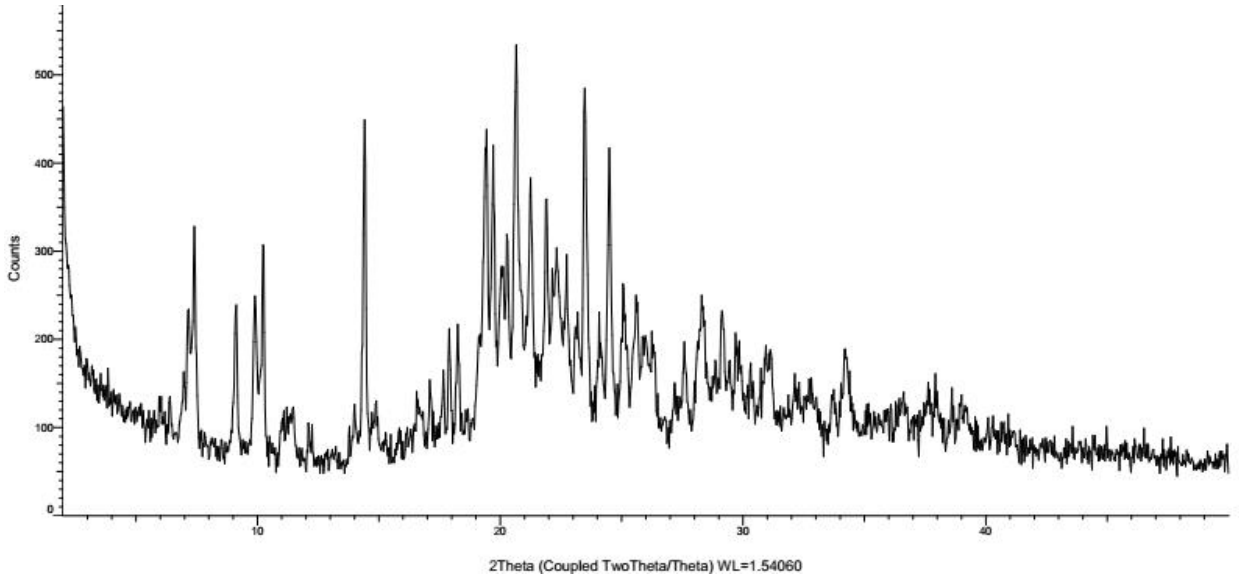


Figure-2

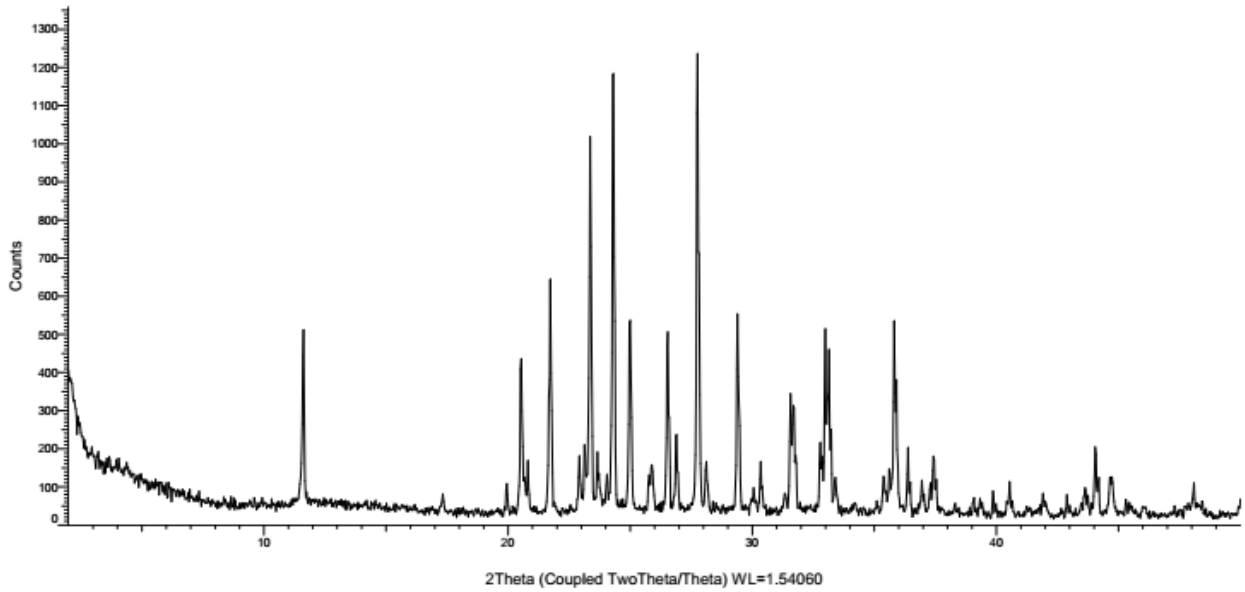


Figure-3

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